

alone. The safety of regimens containing bedaquiline plus delamanid may be substantially improved if clofazimine can be omitted.



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Clofazimine prolongs the QT interval and can potentiate the QT effects of other MDR-TB drugs
<http://ow.ly/70My302XuKm>

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From the authors:

We read with great interest the comments by R.S. Wallis on our article describing the first case of extensively drug-resistant tuberculosis (XDR-TB) treated with both delamanid and bedaquiline [1], as recommended by the European Respiratory Society hosted TB Consilium experts [2, 3].

The patient developed QTc (corrected QT or the measure of time between the start of Q wave and the end of T wave in the heart's electrical cycle (ECG)) prolongation a few days after beginning treatment, that included not only the two new anti-TB drugs but also clofazimine (which, according to Wallis, may have played a role in QTc prolongation). Clofazimine-related cardiotoxicity has been described in a single case-report on an Indian male with leprosy with electrolyte abnormalities treated with clofazimine for 11 months [4]. We agree that there are ongoing safety concerns about QTc prolongation when clofazimine is combined with bedaquiline; safety data remains sparse, although serious life-threatening arrhythmias resulting from this combination have not been described yet.

Our patient had XDR-TB with a single certified active drug, clofazimine, which was the rationale for its inclusion in the salvage regimen. Given the fairly sudden rise in QTc within a week of starting the combination, the TB Consilium experts considered bedaquiline as the culprit for the adverse event. Clofazimine, in fact, requires several weeks to reach the steady state due to its peculiar pharmacokinetics, while bedaquiline at that time was being loaded and, considering its long half-life, the experts recommended to stop it. The patient presented with hypokalaemia during that period, which may have

also potentiated the drug-related QTc prolonging effect. After electrolyte correction, QT prolongation remained within acceptable limits (always below 500 ms), and bedaquiline was therefore restarted (as shown in figure 1) in association with verapamil 40 mg three times daily [1].

However, due to persistence of QTc prolongation and its progressive worsening to 508 ms in week 5 of treatment, the treating physician decided to interrupt clofazimine (as previously recommended by the TB Consilium experts), continuing all the other drugs, including bedaquiline and delamanid. After clofazimine interruption, the patient's QTc has been regularly monitored on weekly basis. After an initial reduction to below 500 ms in week 10, the QTc progressively increased again in week 12 and subsequently reached levels of up to 520 ms. It remained above 500 ms until week 17. The patient always remained completely asymptomatic, so the treating physician decided to continue the treatment without any drug interruption. Electrolytes and albumin levels remained within the normal range. After that, the QTc spontaneously returned to levels below 500 ms, where it stands at the moment. The persistence of prolonged QT up to values above 500 ms after clofazimine interruption suggests that the role of clofazimine in QTc prolongation in our patient was limited.

Despite clofazimine interruption, the interim treatment response is very good as the patient has been persistently sputum smear and culture negative since the second month of treatment.

While it is true that clofazimine is a much older drug that did not undergo today's rigorous testing, recent studies examining data accrued over the past decades have not reported cardiotoxicity with clofazimine used as an anti-TB treatment [5-7]. The actual debates about the risk of cardiotoxicity with clofazimine are related to its frequent association with other QT prolonging drugs (bedaquiline, delamanid, moxifloxacin) in salvage treatment for multidrug-resistant or XDR-TB patients.

It is possible that clofazimine and bedaquiline have a synergic effect and together are more likely to cause QTc prolongation, especially if they are additionally combined with other QT prolonging drugs. Therefore we agree with Wallis that studies are needed to determine if clofazimine potentiates the combined QT prolonging effects of bedaquiline plus delamanid, as it does with bedaquiline alone. However, the conclusion that the safety of regimens containing bedaquiline plus delamanid may be substantially improved if clofazimine can be omitted is questionable and, therefore, a matter for debate.

In our opinion, potential cardiotoxicity should not represent an upfront contraindication for clofazimine use with the new drugs. Given that clofazimine has been found to be active against *Mycobacterium tuberculosis*

	Baseline	Month 1				Month 2				Month 3				Month 4				Month 5				Month 6			
Clinical conditions	Occasional cough with expectoration	Improving Some cough with expectoration				Improving No cough, some expectoration				Improving				Improving				Improving				Improving			
Body weight kg	70	70				69				69.5				69				69				69			
Hospitalisation	October 2015	Yes				Yes				Yes				Yes				Yes				Yes			
Chest radiography	Bilateral upper zones fibro-cavitary lesions									Bilateral upper zones fibro-cavitary lesions															
Sputum smear	Positive	Positive				Negative				Negative				Negative				Negative							
Sputum culture	Positive	Positive				No growth				No growth				Ongoing				Ongoing							
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15	W16	W17	W18	W19	W20	W21	W22	W23	W24
Treatment	Started on 25/02/2016																								
Bedaquiline																									
Delamanid																									
Clofazimine	Hold on 2 April																								
Terizidone																									
Meropenem																									
Amoxicillin/clavulanate																									
Verapamil	Added on 12 March																								
QTc ms	<450	476	486	489	491	508		500	508	491	486		512	491	510	507	520	501	489	497	492				

FIGURE 1 Follow-up clinical information on the first case undergoing joint treatment with delamanid and bedaquiline. Grey shading indicates the weeks in which individual drugs were administered. W: week; QTc: corrected QT or the measure of time between the start of Q wave and the end of T wave in the heart's electrical cycle.

in vitro [8], clinical data including Bangladesh regimen experience support its efficacy [7, 9, 10], and for some patients (as in our case) clofazimine represents the only effective drug, exclusion of clofazimine from salvage therapy would greatly limit treatment efficacy. Patients due to receive a regimen with QT prolonging drugs (*i.e.* bedaquiline, delamanid, clofazimine and moxifloxacin) alone or in combination should receive ECG and electrolytes monitoring before and during treatment, so as not to lose therapeutic benefit. If QTc prolongation above 500 ms occurs, one of the QTc prolonging drugs should be promptly discontinued.



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First case, concerns and challenges of treatment of severe XDR-TB with both delamanid and bedaquiline <http://ow.ly/8e4l303i0LH>

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Tuberculosis prevention must integrate technological and basic care innovation

To the Editor:

ALBERT *et al.* [1] advocate for a multipronged approach in rolling out new diagnostic technology for tuberculosis (TB), stating “diagnostic tests alone, if not implemented with a comprehensive package of accompanying tools and within the context of a strengthened health system, may fail to demonstrate the expected benefit”. This is a lesson learned from those who have walked this path before us; one should not be too complacent to ignore basic strategies in the face of escalating technological advances in our field.



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